



LETTERS TO THE EDITOR

Atypical manifestations of Epstein-Barr virus: red alert for primary immunodeficiencies[☆]



Manifestações atípicas do vírus de Epstein-Barr: alerta vermelho para imunodeficiências primárias

Dear Editor,

The *Jornal de Pediatria* has published an elegant review paper entitled "Atypical manifestations of Epstein-Barr virus in children: a diagnostic challenge".¹ The authors performed a literature review including the last 30 years of publications on atypical manifestations associated with an Epstein-Barr virus (EBV) infection. However, I would like to complement their review by providing a particularly important point of view related to atypical EBV infections.

EBV is a gamma-1 herpes virus restricted to primate hosts, characterized by its persistence in the B-lymphoid system, and its capacity to stimulate B-cells growth by coordinating the expression of latent cycle genes.² Most EBV-infected individuals are asymptomatic or present infectious mononucleosis syndrome with a benign course, especially teenagers and young adults.^{2,3} In its normal course, EBV infects B-cells and the immune system controls the virus using a complex mechanism that involves NK, iNKT, CD4, and CD8 cells. Genetic alterations leading to functional NK or T-cell impairment may lead to a failure in the EBV control mechanisms.³

Primary immunodeficiencies (PIDs) are a group of different diseases that cause alterations in the development and/or function of the immune system, leading to an increased susceptibility to infections and, in some cases, increased incidence of autoimmune diseases and malignancies. Most PID cases are genetic diseases that follow

simple Mendelian patterns of inheritance, while a few others are considered as complex disorders.^{4,5} The advance in the genetic approaches in the last years has increased the pace at which causative genes for PIDs are being discovered.⁵

Recently, Palendira and Rickson, in a educational and simple method, divided PID patients into groups to explain the susceptibility to EBV infections: (1) PIDs that are selectively susceptible to EBV; (2) PIDs with broader virus susceptibility, but frequent EBV disease; (3) PIDs generally susceptible to viral and nonviral infections; and (4) PIDs with an inherent susceptibility to lymphoma.²

Group 1 includes the X-linked lymphoproliferative diseases type 1, caused by SH2D1A gene mutations, and type 2, associated with XIAP gene mutations. In both diseases, patients could present severe infectious mononucleosis; and acute disease could result in a cytokine storm that causes macrophage activation and hemophagocytic lymphohistiocytosis (HLH).^{2,4} In another review, authors added three different PIDs to this group, including mutations in the genes PRF1 (perforin deficiency, autosomal recessive (AR)), STXBP2 (munc18-2 deficiency, AR), and UNC13D (munc13-4 deficiency, AR), which are also associated with HLH and the development of chronic and severe EBV disease.⁶

Group 2 contains PIDs caused by mutations in genes CD27 (CD27 deficiency, AR), MAGT1 (XMEN syndrome, X-linked), ITK (ITK deficiency, AR), CORO1A (coronin-1A deficiency, AR), FCGR3 (CD16 deficiency, AR), and MCM4 (MCM4 deficiency, AR).² The diseases in this group showed an increased susceptibility not only to EBV, but also to other herpes virus family and, in some cases, to HPV.⁴

Group 3 has complex PIDs with different predispositions to several microorganisms, including EBV infections. The PIDs included in this group are result of mutations in genes PIK3CD (Activated PI3-kinase delta syndrome, autosomal dominant (AD)), STK4 (MST1 deficiency, AR), ZAP70 (Zap-70 deficiency, AR), CTPS1 (CTPS1 deficiency, AR), CARD11 (CARD11 deficiency, AR), LRBA (LRBA deficiency, AR), GATA2 (mono MAC syndrome or GATA2 deficiency, AD), LYST (Chediak-Higashi syndrome, AR), and hypomorphic mutations in ARTEMIS and DNA ligase IV, both associated with Omenn syndrome.^{2,4,6}

The PIDs in group 4 present different degrees of immune system deficiency, which are also associated with increased

DOI of original article:

<http://dx.doi.org/10.1016/j.jpmed.2015.06.007>

[☆] Please cite this article as: Segundo GR. Atypical manifestations of Epstein-Barr virus: red alert for primary immunodeficiencies. J Pediatr (Rio J). 2016;92:539–40.

cancer incidence and the involvement of EBV in some of these tumors, especially lymphomas. This group includes PIDs with mutations in genes WAS (Wiskott–Aldrich syndrome, X-linked), ATM (Ataxia telangiectasia syndrome, AR), and TNFRSF6 (ALPS-FAS, AD and AR).^{2,4,6}

The message for all pediatricians is to consider EBV as a causative agent in clinical pictures similar to those described by Bolis et al. In addition to the immune system impairment associated with treatment for several diseases, we must also consider these situations as a red alert for primary immunodeficiencies in pediatric patients. Recognizing PIDs may be essential to achieve a better management for patients with atypical EBV infections.

Funding

C.H.I.L.D.R.E.N. initiative for primary immunodeficiency research of the Jeffrey Modell Foundation; Postdoctoral Fellow abroad through Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – CAPES (Higher Education Personnel Improvement Coordination).

Conflicts of interest

The author declares no conflicts of interest.

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<http://dx.doi.org/10.1016/j.jped.2016.05.002>

Authors' reply: Atypical manifestations of Epstein-Barr virus: red alert for primary immunodeficiencies[☆]



Resposta dos autores: manifestações atípicas do vírus de Epstein-Barr: alerta vermelho para imunodeficiências primárias

Dear Editor,

Human primary immunodeficiency disease (PID) is a condition where mutations in single immune system genes predispose individuals to certain infectious agents. The human herpesviruses are a challenge of immune competence, since most of these agents are widespread in the population; they are often acquired silently or with mild symptoms in childhood and then carried for life as asymptomatic latent infections. PID patients are therefore likely to be exposed to these viruses relatively early in life and will have to deal with them both as a primary infection

and as a persistent condition.¹ For individuals who are immunocompromised, due to a genetic immunodeficiency or immunosuppressive drug therapy, viral infections may result in severe complications and even life-threatening disease.²

PID is considered a rare disease, with an overall incidence of 4.6 cases of PIDs per 100,000 person-years in the last 35 years.³ However, neither the true incidence nor the true prevalence of PID are known. Although there have been estimates of these parameters from geographically limited studies, those estimates were based only on diagnosed cases. Therefore, PID may be far more common than previously estimated. Surveys suggest prevalence rates for diagnosed PID as 1:2000 for children, 1:1200 for all persons, and 1:600 households.⁴

Specific gene mutations in PID patients are responsible for susceptibility to Epstein-Barr virus (EBV) infections, as highlighted in the letter to the editor of the *Jornal de Pediatria* entitled "Atypical manifestations of Epstein-Barr virus: red alert for primary immunodeficiencies". Although PID and atypical complications of EBV infection are not very common, pediatricians should indeed correlate these two conditions as mentioned in the previous letter, since EBV infects more than 95% of the adult population worldwide.⁵ PID incidence has increased in the last decades,³ and patients with immunodeficiency are the group most exposed to atypical complications of EBV among healthy people.

The strongest predictor of PID is family history. Moreover, when an immunodeficiency disease is suspected, initial laboratory screening should include a complete blood count with

DOI of refers to article:

<http://dx.doi.org/10.1016/j.jped.2016.05.002>

[☆] Please cite this article as: Bolis V, Karadedos C, Chiotis I, Chaliasos N, Tsabouri S. Authors' reply: Atypical manifestations of Epstein-Barr virus: red alert for primary immunodeficiencies. *J Pediatr (Rio J)*. 2016;92:540–1.